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## Clinical Study

# High Prevalence of Associated Birth Defects in Congenital Hypothyroidism

**P. Amaresh Reddy,<sup>1</sup> G. Rajagopal,<sup>1</sup> C. V. Harinarayan,<sup>1</sup> V. Vanaja,<sup>2</sup> D. Rajasekhar,<sup>2</sup> V. Suresh,<sup>1</sup> and Alok Sachan<sup>1</sup>**

<sup>1</sup> Department of Endocrinology and Metabolism, Sri Venkateswara Institute of Medical Sciences, Tirupati 517507, India

<sup>2</sup> Department of Cardiology, Sri Venkateswara Institute of Medical Sciences, Tirupati 517507, India

Correspondence should be addressed to Alok Sachan, [alok\\_sachan@rediffmail.com](mailto:alok_sachan@rediffmail.com)

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**Aim.** To identify dysmorphic features and cardiac, skeletal, and urogenital anomalies in patients with congenital hypothyroidism. **Patients and Methods.** Seventeen children with congenital primary hypothyroidism were recruited. Cause for congenital hypothyroidism was established using ultrasound of thyroid and <sup>99m</sup>Tc radionuclide thyroid scintigraphy. Malformations were identified by clinical examination, echocardiography, X-ray of lumbar spine, and ultrasonography of abdomen. **Results.** Ten (59%) patients (6 males and 4 females) had congenital malformations. Two had more than one congenital malformation (both spina bifida and ostium secundum atrial septal defect). Five (29%) had cardiac malformations, of whom three had only ostium secundum atrial septal defect (ASD), one had only patent ductus arteriosus (PDA), and one patient had both ASD and PDA. Seven patients (41%) had neural tube defects in the form of spina bifida occulta. **Conclusion.** Our study indicates the need for routine echocardiography in all patients with congenital hypothyroidism.

## 1. Introduction

Congenital hypothyroidism is one of the common and readily preventable causes of mental retardation. Prevalence of sporadic congenital hypothyroidism is 1 in 2500–4000 [1, 2]. In India the prevalence has been reported to be 1 in 2640 [2]. National neonatal screening programs are in place in developed countries to facilitate early diagnosis and treatment to prevent irreversible sequelae, that is, short stature and mental retardation [3–6]. Unfortunately there is no such ongoing program, nor is there any detailed registry of congenital hypothyroidism patients in India.

There are reports of a high prevalence of associated congenital anomalies ranging from congenital heart disease to neural tube defects in this population [7–11]. However, the prevalence of these has been variable in the different ethnic groups [12–14]. A high frequency of birth defects suggests the possible role of common genes or intrauterine factors in multiple organ differentiation, including the

thyroid. Indeed there is some evidence to suggest that defects in genes involved in thyroidogenesis can also cause cardiac anomalies [15, 16].

No data on the prevalence of common birth defects in patients with congenital hypothyroidism is available from India. We planned this study to rigorously and systematically identify and document dysmorphic features cardiac, skeletal, and urogenital anomalies in patients of congenital hypothyroidism being followed up in our pediatric endocrinology clinic.

## 2. Methodology

This ongoing cross-sectional study is being conducted in patients diagnosed to have congenital hypothyroidism, being followed up in Pediatric Endocrinology Clinic, Sri Venkateswara Institute of Medical Sciences, Tirupati, a tertiary care centre.

TABLE 1: Extrathyroidal congenital malformations in patients with congenital hypothyroidism.

No. of malformations associated with congenital hypothyroidisms	Age in years	Sex	Cause of congenital hypothyroidism	Congenital heart disease	Spinal anomalies (on X-ray)
1	1	M	Agenesis	Ostium secundum ASD (5 mm)	Absent
2	4	M	Agenesis	Absent	Spina bifida of L5
3	4	F	Agenesis	Absent	Spina bifida of L5 and S1
4	12	F	Agenesis	Ostium secundum ASD (13 mm)	Spina bifida of S1
5	4.5	F	Ectopic thyroid in upper neck	3 mm PDA	Absent
6	0.25	M	Agenesis	Ostium secundum ASD (3 mm) and PDA (2 mm)	Absent
7	14	M	Agenesis	Absent	Spina bifida of S1
8	14	M	Dyshormonogenesis	Ostium secundum ASD (17 mm)	Spina bifida of L5
9	12	M	Dyshormonogenesis	Absent	Spina bifida of L5
10	0.5	F	Agenesis	Absent	Spina bifida of S1

**2.1. Subjects.** All children presenting to our clinic with biochemically confirmed primary hypothyroidism (low triiodothyronine, low thyroxine, and thyrotropin  $>10$  IU/mL) having an early infantile or neonatal onset of symptoms, such as delayed developmental milestones, short stature, mental retardation, and so forth, consistent with a congenital origin of the hypothyroidism were recruited into the study. In all recruited patients, a  $^{99m}\text{Tc}$  radionuclide thyroid scintigraphy was performed using anterior, right anterior oblique, left anterior oblique views, and those showing agenesis, hemiagenesis, and ectopic thyroid tissue or those consistent with dyshormonogenesis were considered to be truly congenital in origin. In our patients dyshormonogenesis was diagnosed in those patients who had an early childhood onset large goiter with increased technetium uptake despite the presence of gross hypothyroidism.

Malformations were identified based on clinical examination, echocardiography, X-ray of hand and lumbar spine, and ultrasonography of abdomen and pelvis. The clinical examination included looking for the presence of dysmorphic features, spinal defects, and cardiac murmurs. Two-dimensional echocardiography, M-mode, pulsed-wave and continuous-wave Doppler, and color flow mapping were done with Philips sono with 2.5 to 10 MHz transducers. A search for associated congenital anomalies, any valvular lesion, or myocardial involvement with routine measurement of left ventricular dimensions, function, and other cardiac chamber dimensions was done. Thyroid, abdominal, and pelvic ultrasound was done using digital Philips with a 5 MHz convex probe in the fasting patient. Abdominal sonogram evaluation was done for the presence of congenital anomalies particularly urogenital malformations.

**2.2. Biochemistry.** TSH estimation was done using a commercial IRMA (BARC, Mumbai) kit (range of measurement 0.15–50.0  $\mu\text{IU/mL}$ ).

**2.3. Results.** Among the seventeen patients identified there were 9 males and 8 females. Ages ranged from 6 months to 17 years. All of them had a high TSH ( $>50$   $\mu\text{IU/mL}$ ) at diagnosis. The etiology of congenital hypothyroidism was ascertained by thyroid ultrasound and thyroid scintigraphy. Eleven children had agenesis, one had hemiagenesis of left lobe, one had ectopic thyroid, and four had dyshormonogenesis. Ten (59%) patients (6 males and 4 females) had congenital malformations (Table 1).

Two had congenital malformations involving more than one organ (both spina bifida and ostium secundum atrial septal defect in two patients). Five (29%) had cardiac malformations, of whom three had only ostium secundum atrial septal defect (ASD), one had only patent ductus arteriosus (PDA), and one had both ASD and PDA. The size of the ASDs ranged from 3 to 17 mm with left to right shunt with no pulmonary arterial hypertension. The child with 17 mm ASD underwent a percutaneous device closure. Of the three with ASD, two had thyroid agenesis and one had dyshormonogenesis. The patient with isolated PDA (3 mm in size) had an ectopic thyroid gland whereas the one with combined PDA (2 mm size) and ASD (3 mm size) had thyroid agenesis. The former is awaiting a device closure for her PDA.

Seven patients (41%) had neural tube defects in the form of spina bifida occulta (three in the fifth lumbar vertebra, three in the first sacral vertebra, and one had spina bifida at L5 and S1), seen only on X-ray of the lumbar spine.

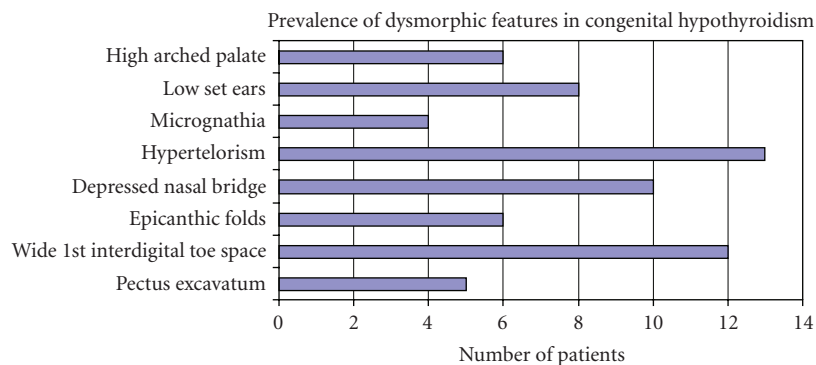


FIGURE 1: Prevalence of dysmorphic features in congenital hypothyroidism.

None of the patients had any congenital abnormality on abdominal sonography. Most of the children (94%) examined had some dysmorphic features in the form of hypertelorism, wide first toe web space, pectus excavatum, epicanthic folds, depressed nasal bridge, micrognathia, low set ears, and high arched palate (Figure 1).

### 3. Discussion

The high prevalence of dysmorphic features (94%), congenital heart disease (29%), and spina bifida occulta (41%) in our patients points to the fact that congenital hypothyroidism may not be an isolated event but rather a part of larger developmental syndrome resulting from some unknown insults during early embryogenesis. To our knowledge this is the first study ever to report the prevalence of dysmorphic features in this disease from India.

The prevalence of congenital heart disease in our study is 29% which is very high compared to the prevalence in the general population in our country. Kapoor and Gupta [17] observed a prevalence of congenital heart disease to be 2.64% in a retrospective clinic-based study. Clinical examination, echocardiography, and colour Doppler were used as diagnostic tools. Smitha et al. [18] by collecting data from three hospitals in Mysore by retrospective evaluation of the hospital records reported a prevalence of congenital heart disease (diagnosed on clinical examination complimented by echocardiography) to be varying between 0.66% and 1.36%. In a prospective study of all live newborns born at a single centre, Khalil et al. [19] reported an incidence of only 3.9 per thousand live births. Diagnosis was confirmed by echocardiography including 2D, Doppler, and colour flow imaging. Other community-based studies have revealed a prevalence of 0.8 to 4.2 per 1000 children [20].

In a prospective study by Kholy et al. [14] the prevalence of congenital heart disease in newborn screened children with CH was 9.09%. The prevalence of cardiac malformations (on echocardiography) in a similar prospective study carried out between 2004 and 2005 in newborns screened for CH in Isfahan, Iran by Sabri et al. [21] was 6.25% in patients with congenital hypothyroidism versus only 1.7% in euthyroid controls after the exclusion of patent foramen

ovale. Thyroid scintigraphy and/or ultrasonography were performed in all patients.

Balestrazzi et al. [13] on retrospectively analyzing the Italian National Registry for congenital hypothyroidism (ultrasound imaging, scintigraphy, and clinical examination were used to establish the etiology of CH) for the years 1987–1992 found that the birth defect incidence (as based on written descriptions of all congenital malformations in the registry) was higher in patients with CH than in the general population (4.3% versus 2.5%–3%) and especially the incidence of cardiac malformations (2.1% versus 0.3%–0.8%). The most frequent cardiac malformations observed by Balestrazzi et al. [13] were septal defects and Pulmonic Stenosis (PS). In a later retrospective review of the same registry for infants diagnosed during the period 1991–1998 Olivieri et al. [12] found cardiac anomalies in 5.5% of patients with CH. Kreisner et al. [22] evaluated major congenital malformations in their prospective clinic-based study of CH ( $n = 76$ ) from Brazil. They used ultrasonography and thyroid scintigraphy to establish the cause of CH while the malformations were evaluated by clinical examination. In those with clinical signs of cardiac malformation one-dimensional and two-dimensional echocardiography studies with Doppler and colour flow mapping were performed. Nine patients had normally placed and shaped glands, while there were 67 cases of dysgenesis (42 cases of agenesis, 24 cases of ectopia, and 1 case of hemiagenesis). Ten patients (13.2 %) had major congenital malformations of which 8 (10.5% of the total) had cardiac malformations. Gu et al. [23] carried out a retrospective review of questionnaires based on the medical records of each patient of CH in the first year of life. There were a total of 1520 babies with CH born between April 1994 and March 2003. They reported extrathyroidal congenital malformations in 14.6%. Cardiac congenital malformations were seen in 8.9%. A higher incidence of congenital cardiac and nervous system malformations (versus the nationwide incidence in all live-born children in Japan) was found in a female predominant manner among those patients of CH who did not have Down's syndrome.

Our study showed a high prevalence of ASD and isolated cases of PDA and combined ASD and PDA. The observed

wide difference in the prevalence of cardiac malformations in our patients versus those reported from other countries may reflect ethnic differences in genetic factors or unknown adverse intrauterine environmental exposures involved in congenital hypothyroidism. These findings need to be reconfirmed in a larger cohort of congenital hypothyroidism. Further studies of genetic and other etiological factors need to be performed in the Indian population to identify those factors linking congenital hypothyroidism with congenital heart disease.

Unlike other studies [12–14], our study did not show urogenital anomalies, probably because of small numbers studied.

Several studies have shown that genetic factors may be involved in the pathogenesis of congenital hypothyroidism (CH). It has been reported that mutations in the genes encoding transcription factors (*TTF1*, *TTF2*, and *PAX8*) or the TSH receptor cause thyroid dysgenesis in humans or in mouse models [15, 16]. *TTF-1* and *TTF-2* have been redesignated as *NKX2-1* (OMIM 600635) and *FOXE 11* (OMIM 602617), respectively. Moreover, a familial clustering, of athyreosis and ectopic thyroid gland has been reported [24]. This finding strongly suggests the potential involvement of genetic factors, including other genes that are as yet unknown. Again, the significantly higher frequency of extrathyroidal congenital malformations reported in the CH infants than in the general population represents a further argument supporting the role of a genetic component in the etiology of CH. Our study, although small in numbers, shows that congenital hypothyroidism is associated with multiple congenital malformations predominant being cardiac, neural tube defects and dysmorphic features.

The high frequency of multiple congenital anomalies found in the population of CH children suggests an early impairment in embryonal development with a consequent involvement of different organs and structures. The significant association between CH and anomalies of nervous system, eyes, and heart fits well with results obtained in studies conducted in experimental models. In these studies, anomalies occurring in organs that are dependent on neural crest cells for their development were hypothesized to result from a disturbance of the proliferation and migration of the neural crest cells in the early phases of embryonal development [25–28]. These cells represent a migratory cell population derived from the dorsal neural tube that contributes to a wide variety of tissues throughout the embryo. Studies of avian and mouse embryos demonstrated that a neural crest subpopulation, termed cardiac neural crest, plays a vital role in the normal heart morphogenesis and contributes cells to the aortic arches, thymus, thyroid, and parathyroids [28, 29]. Ablation studies in the chick have also demonstrated the occurrence of cardiac outflow tract defects frequently in association with defective or absent thymus, thyroid, and parathyroids [25, 30]. In our study cardiac anomalies and neural tube defects were the most frequent congenital malformations observed in CH.

It is important to recognize the fact that embryonic thyroid development is closely associated with the developing heart. The thyroid is pulled to its position near the base of

the neck as a consequence of the continuing descent of the heart during the early stages of thyroid formation [31]. It has been reported that mutations in genes that control thyroid development are associated with some cardiac congenital malformations [32]. *NKX2.5* (OMIM 600584) is a novel gene involved in the pathogenesis of congenital hypothyroidism with ectopy or athyreosis of the thyroid gland [33]. Many point mutations have been identified in *NKX2.5* transcription factor in families with atrial septal defects [34]. Sporadic mutations of *NKX2.5* have also been found in patients with tetralogy of Fallot [35]. Again, recent studies conducted in experimental models have implicated the homeobox gene *HEX* (OMIM 604420) in the development of the cardiovascular system and the thyroid gland [36, 37]. In the light of this evidence, investigations on the molecular mechanisms underlying the developmental events of heart and thyroid and understanding how perturbations of possible common developmental control genes may result in thyroid dysgenesis and in different forms of congenital heart disease represent critical steps in understanding the congenital hypothyroidism.

Our ongoing study has showed a very high prevalence of congenital heart disease in congenital hypothyroidism, indicating the need of routine echocardiography in all patients with congenital hypothyroidism, for early diagnosis and management.

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